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Obesity's Influence on Insulin Resistance in Pregnant Women with Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is a common endocrine metabolic disorder that is associated with high insulin resistance and obesity. However, ~70% of women with PCOS in Japan are non-obese. We retrospectively analyzed the cases of 163 Japanese women with PCOS who visited our Ob/Gyn department in 2006-2018 to determine which has a greater effect on insulin resistance: PCOS or obesity. We reviewed the women's medical records and calculated their insulin resistance and insulin secretion. The women's mean age and pre-pregnancy body mass index (BMI) were 30 ± 5.8 years and 24.8 ± 5.6 kg/m^2, respectively;   their mean $\pm$ SD fasting plasma glucose, 94.1 ± 13.7 mg/dL; HOMA-IR, 2.1 ± 2.0; QUICKI, 0.4 ± 0.0; and HOMA-β, $108.9 \pm 88.0\%$. Sixty-eight women were pregnant, and 37% (n = 25) were obese (BMI ≥ 25 kg/m^2). Obesity had a greater effect on insulin resistance: fasting plasma glucose $F(1, 53) = 6.134$, $p < 0.05$; fasting insulin $F(1, 53) = 31.606$, $p < 0.01$; HOMA-IR $F(1, 53) = 31.670$, $p < 0.01$; QUICKI $F(1, 53) = 16.156$, $p < 0.01$. There was no significant difference in values other than QUICKI and testosterone between the women with and without PCOS. Obesity thus had a greater effect on increased insulin resistance in pregnant women with PCOS. Further studies of the insulin resistance of non-obese women with PCOS is needed, as non-obese women with PCOS are common in Asia.

Key words: polycystic ovary syndrome, insulin resistance, obesity, pregnancy

P olycystic ovary syndrome (PCOS) is a common endocrine metabolic disorder that affects 5-15% of women of reproductive age [1]. Women with PCOS have an increased risk of experiencing insulin resistance [2,3], and insulin resistance and hyperinsulinemia are recognized as common features of PCOS. Obesity plays an important role in the pathophysiology of PCOS; it also enhances insulin resistance, resulting in hyperinsulinemia [4]. The percentage of obese women with PCOS differs between Western countries and Asian countries; for example, approx. 40% of women with PCOS in the U.S. are obese, whereas only ~25% of the women with PCOS in Japan are obese. It is not yet understood why non-obese women with PCOS are at the same high risk of developing insulin resistance as obese women with PCOS.

Several studies have demonstrated increased risks of hypertensive disorders in pregnancy (HDP), gestational diabetes (GDM), and preterm labor (PTL) in pregnant women with PCOS [5,6]. The data adjusted for body mass index (BMI) were recently reported, and the association between PCOS and perinatal outcomes such as higher miscarriage, GDM, HDP, delivery induction, and caesarean section varied by the subjects' pre-BMI and PCOS phenotypes [7]. An analysis of BMI-matched studies revealed that preeclampsia and the induction of delivery were not associated with PCOS

[8]. The higher risks of GDM and glucose metabolism impairment among pregnant women with PCOS were also influenced by their pre-BMI levels [9]. We conducted the present study to determine whether PCOS or obesity has a greater effect on insulin resistance.

Subjects and Methods

Ethical approval. This study was conducted after obtaining permission from the Research Ethics Committee of the Okayama University Medical Department. Due to the retrospective nature of the study, the requirement for subjects' informed consent was waived.

Subjects. We analyzed the cases of the 163 Japanese women with PCOS who visited the Okayama University Hospital Department of Obstetrics and Gynecology (Okayama, Japan) during 2006-2018. Non-PCOS pregnant women matched for age, gestational age, and BMI with normal pregnancies who visited our hospital during the same period were included as controls (n=68). Women with pre-existing diabetes and hypertension were excluded. The planned sample size of 68 pregnant women with and without PCOS was based upon 80% power, 0.05 significance level, and 0.5 effect size.

Variables. PCOS was defined according to the criteria of the Japanese Society of Obstetrics and Gynecology including three main features: (1) menstrual cycle irregularities, (2) polycystic changes in an ovary observed on ultrasonography, and (3) endocrine anomalies (luteinizing hormone or androgen hypersecretion) [10]. Obesity was defined as a BMI > 25 kg/m^2. Insulin resistance was defined as the presence of a homeostasis model assessment of insulin resistance index (HOMA-IR) value > 2.5 or a quantitative insulin sensitivity check index (QUICKI) value < 0.33.

Measurements. All of the subjects' values were measured preconception. Fasting insulin was measured by a fluorescence enzyme immunoassay (Tosoh Corp., Tokyo), and glucose levels was measured by the glucose oxidase method (Shino-Test Corp. Tokyo). Insulin resistance was measured using the following equations: HOMA-IR=fasting glucose level (mg/dL)×fasting insulin level (μU/mL)/405 and QUICKI=1/[log fasting insulin level (μU/mL)+log fasting glucose level (mg/dL)]. Insulin secretion was indicated by the HOMA of β-cell function (HOMA-β) (%)=360×fasting insulin

level (μU/mL)/[fasting glucose level (mg/dL) − 63] [11].

Statistical analysis. This was a retrospective cohort study. Continuous data are expressed as the mean ± standard deviation (SD), and categorical data are presented as percentages. Significant differences in the subjects' ages and clinical parameters were evaluated using Student's *t*-test. The χ^2-test was used for intergroup comparisons of the percentage of perinatal complications. The associations of BMI with HOMA-IR, QUICKI, and HOMA-β were analyzed using Spearman's rank correlation. The effect of PCOS or obesity on insulin resistance was evaluated by a two-way analysis of covariance (ANCOVA). *P*-values < 0.05 were considered significant.

Results

The subjects' characteristics are summarized in Table 1. Their preconception BMI was 24.8 ± 5.6 kg/m^2. Fifty-five of the 163 women with PCOS (34%) were obese; the other 108 (66%) were non-obese. The HOMA-IR, QUICKI, HOMA-β, and testosterone values of the women with PCOS were all higher than the normal ranges.

The outcomes of the pregnancies and the pregestational interventions are listed in Table 2. Sixty-eight (42%) pregnancies were singleton, and 30 required ovulation induction. Table 3 provides the results of the

Table 1   Characteristics of all PCOS participants (n=163)

Age (y)	30 ± 5.8	
BMI at preconception (kg/m^2)	24.8 ± 5.6	
Obese; BMI ≧ 25 kg/m^2 (n)	55 (34%)	
Non-obese; BMI < 25 kg/m^2 (n)	108 (66%)	
FPG (mg/dL)	94.1 ± 13.7	
Fasting IRI (μU/mL)	8.9 ± 7.3	[2.1−19.0]
HOMA-IR	2.1 ± 2.0	[≦ 1.6]
QUICKI	0.4 ± 0.0	[> 0.33]
HOMA-β (%)	108.9 ± 88.0	[40−60]
LH (mIU/mL)	7.6 ± 5.8	
FSH (mIU/mL)	6.3 ± 2.1	
Testosterone (ng/dL)	64.4 ± 27.4	[9−56]
HbA1c (%)	5.5 ± 0.6	

PCOS, polycystic ovary syndrome; BMI, body mass index; FPG, fasting plasma glucose; IRI, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance index; HOMA-β, homeostasis model assessment beta; LH, luteinizing hormone; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; QUICKI, quantitative insulin sensitivity check index. The parentheses indicate the reference range.

comparison between the pregnant women with and without PCOS who were matched for age, gestational age, and preconception BMI: there was no significant difference in characteristics between the PCOS and non-PCOS pregnant women except for QUICKI and testosterone values. QUICKI was significantly lower and testosterone was higher in the PCOS group.

The results of our comparison of the obese and non-obese pregnant women with PCOS is shown in Table 4. In both the PCOS and non-PCOS groups, the fasting plasma glucose (FPG), fasting insulin (IRI), HOMA-IR, HOMA-β, triglycerides, and neonatal birth weight were higher and the QUICKI was lower in the obese women compared to the non-obese women. There was no significant difference between the obese and non-obese women in maternal age, gestation week and percentage

of perinatal complications. In non-PCOS group, testosterone was higher in obese than non-obese pregnant women.

The results of the statistical analyses of the effect of PCOS and the effect of obesity on insulin resistance are shown in Table 5. Compared to PCOS, obesity had a greater effect on insulin resistance: FPG $F(1,53) = 6.134$, $p < 0.05$; fasting IRI $F(1,53) = 31.606$, $p < 0.01$; HOMA-IR $F(1,53) = 31.670$, $p < 0.01$; QUICKI $F(1,53) = 16.156$, $p < 0.01$. PCOS showed no significant effect, with the exception of its influence on the QUICKI and testosterone values.

Discussion

In general populations of pregnant women, the prevalence of insulin resistance has been reported as 44-85% [12,13]. This wide variation in the prevalence is due in part to differences in PCOS phenotypes and ethnicity [2]. Enes *et al.* reported that the two phenotypic combinations of 'hyperandrogenism, oligo/anovulation, and PCOS appearance' and 'hyperandrogenism and oligo/anovulation' led to the highest risk of metabolic syndrome [10]. In our present investigation, there were no significant differences between the preg-

Table 2　Prognosis of pregnancy and pregestational interventions

Successful singleton pregnancies	68 (42%)
Ovulation induction	30 (44%)
Metformin	16 (24%)
Laparoscopic ovary drilling	5 (7%)
Miscarriages	19 (12%)
No pregnancy	76 (46%)

Table 3　Comparison between PCOS pregnant women and non-PCOS matched for age, gestational age and BMI at preconception

	PCOS (n=68)	Non-PCOS (n=68)	P
Age (y)	31.3 ± 4.8	31.8 ± 5.0	NS
BMI at preconception (kg/m^2)	24.5 ± 5.1	25.5 ± 5.8	NS
Obese; BMI ≧ 25 kg/m^2 (cases)	25 (37%)	25 (37%)	NS
Non-obese; BMI < 25 kg/m^2 (cases)	43 (63%)	43 (63%)	NS
FPG (mg/dL)	94.8 ± 12.2	93.3 ± 13.0	NS
Fasting IRI (μg/mL)	9.4 ± 8.4	9.6 ± 8.0	NS
HOMA-IR	2.2 ± 2.2	1.7 ± 1.9	NS
QUICKI	0.36 ± 0.04	0.39 ± 0.05	<0.05
HOMA-β (%)	115.1 ± 107.1	89.9 ± 63.2	NS
Testosterone (ng/dL)	57.6 ± 21.5	50.3 ± 25.0	<0.05
LDL-C	113.5 ± 25.6	116.4 ± 29.8	NS
TG	91.7 ± 73.9	96.7 ± 60.1	NS
Gestation week	38.3 ± 2.6	38.0 ± 2.3	NS
Birth weight (g)	2,886 ± 576	2,822 ± 469	NS
Perinatal complications (cases)	19 (27.9%)	20 (29.4%)	NS
PTL	8	7	
HDP	1	5	
GDM	6	2	
FGR	4	6	

LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; PTL, preterm labor; HDP, hypertensive disorder of pregnancy; GDM, gestational diabetes mellitus; FGR, fetal growth restriction.

Table 4   Comparison between obese and non-obese pregnant women with PCOS

	Obese (n = 25)	Non-obese (n = 43)	P
Age (y)	30.6 ± 5.7	31.6 ± 4.3	NS
BMI at preconception (kg/m^2)	30.2 ± 4.2	21.6 ± 2.2	<0.01
FPG (mg/dL)	101.1 ± 17.5	91.4 ± 6.1	<0.01
Fasting IRI (μg/mL)	16.1 ± 11.0	6.0 ± 3.6	<0.01
HOMA-IR	4.0 ± 2.9	1.4 ± 0.8	<0.01
QUICKI	0.33 ± 0.04	0.46 ± 0.55	<0.01
HOMA-β (%)	187.0 ± 148.3	79.1 ± 51.7	<0.01
Testosterone (ng/dL)	50.8 ± 19.3	61.0 ± 22.0	NS
LDL-C	121.6 ± 27.0	109.3 ± 24.1	NS
TG	148.5 ± 97.6	61.3 ± 27.1	<0.01
Gestation week	38.4 ± 2.8	38.3 ± 2.5	NS
Birth weight (g)	3,077 ± 402	2,816 ± 532	<0.01
Perinatal complications (cases)	11 (32.0%)	11 (25.6%)	NS
PTL	3	5	
HDP	0	1	
GDM	3	3	
FGR	2	2	

Table 5   Comparing the effect of obesity and PCOS on insulin resistance among 136 pregnant women (included PCOS and non-PCOS, obese and non-obese showed in Table3) by 2-way ANOVA

	PCOS			Obesity		
Dependent variable	Df	F value	P	Df	F value	P
FPG (mg/dL)	1,53	1.559	NS	1,53	6.134	<0.05
Fasting IRI (μg/mL)	1,53	1.387	NS	1,53	31.606	<0.01
HOMA-IR	1,53	1.263	NS	1,53	31.670	<0.01
QUICKI	1,53	8.294	<0.01	1,53	16.156	<0.01
HOMA-β (%)	1,53	0.617	NS	1,53	19.236	<0.01
Testosterone	1,53	13.848	<0.01	1,53	0.552	NS

nant women with PCOS and without PCOS in insulin resistance, insulin secretion, or perinatal complications; the only significant between-group differences were in the values of testosterone and the QUICKI. This may be due in part to the use of BMI matching for the subjects.

Obesity is a common feature of PCOS and contributes to insulin resistance [14]. The percentage of obese individuals in general is lower in Asian than in Western countries. In the present study, 34% of the women were obese. The increased risk of GDM in women with PCOS has been described; GDM is independently associated with adiposity, age (≥ 35 years), own preterm birth, the subject's mother's history of GDM, and a parental history of type 2 diabetes mellitus [15]. Women with PCOS have also been reported to be at a higher risk for HDP [16,17], but this association was

not independent of weight status.

Among the present study's obese pregnant women, the testosterone values were not significantly different between the women with and without PCOS. However, among the non-obese women, the testosterone levels of the pregnant women with PCOS were significantly higher than those of the women without PCOS. Moreover, in the non-PCOS group, the testosterone values of the obese pregnant women were higher than those of the non-obese women. These results demonstrate that PCOS and obesity are key aspects of hyperandrogenism.

A systematic review and meta-analysis revealed that the prevalence of hyperandrogenism was 10-20% in Europe and the U.S. and <10% in Asia [18]. As the clinical presentation of Japanese women with PCOS differs from those in Europe and the U.S. (with a lower

frequency of hyperandrogenism), we defined PCOS according to the criteria of the Japanese Society of Obstetrics and Gynecology instead of The Criteria of Rotterdam [19].

Pregnant obese women with PCOS are considered to be high-risk patients because insulin resistance can cause perinatal complications. Several studies have reported high risks of maternal and fetal complications in obese women. Pre-pregnancy obesity is associated with hyperglycemic disorders, hypertensive disorders, cesarean deliveries, fetal macrosomia, and the umbilical cord pH [20]. Infants born to obese mothers have longer hospital stays [21]. These associations might be influenced by the mother's pre-pregnancy BMI. Women with PCOS, especially those with obesity, are more likely to have a high-risk pregnancy.

Pregnancy complications can be decreased by a healthy lifestyle. The risk of pregnancy complications in women with PCOS was lower in those who did not have alcohol or smoking habits but were participating in vigorous exercise and taking multivitamins [22]. In obese women, the distribution of body fat is one of the risk factors of metabolic disorder. Metabolically unhealthy obese individuals are characterized by a lower subcutaneous fat mass, adipocyte hypertrophy, a pro-inflammatory adipose tissue phenotype, and impaired fat storage capacity of adipose tissue, of all which contributes to the development of insulin resistance and chronic cardiometabolic diseases [23]. Weight reduction interventions could improve the prognosis of pregnancy in obese women with PCOS. Obese women with PCOS are often taking metformin before a pregnancy. Such conditions may have affected the comparable rates of GDM between our present study's obese and non-obese pregnant subjects.

This study has two limitations. First, our data were obtained from a single medical facility in Japan, with the inclusion of only a small number of participants with PCOS. Second, the body fat distribution in the obese participants was not considered. Further research including body construction data is needed to evaluate the influence of obesity in women with PCOS.

In conclusion, obesity has a major effect on increased insulin resistance in pregnant women with PCOS. Additional investigations of insulin resistance in non-obese women with PCOS are necessary, as there are many non-obese women with PCOS in Asian countries.

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